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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,366	03/26/2004	J. Yun Tso	05882.0114.NPUS01	3678

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,366	TSO ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2007 and 19 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The disclosure is objected to because of the following informalities: the imbedded active hyperlinks on page 14 are an impermissible incorporation by reference of the information on the referenced web page and deletion of elements which make them active, including deletion of "http://", is required; page 24, line 7, it is believed --cytochrome-- was intended; page 26, line 11, it is believed --avenue-- was intended. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claim 40 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. Applicant specifically claims and/or requires the 3B10, 4B2, 10, 17, 24, 25, 26, 27, 31, 41, 50, 60, 87, 3-4A, and 3-11F antibodies.

The specification is objected to and claims 39-51 and 53-55 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and

failing to provide an enabling disclosure, because the specification does not provide evidence that the biological materials required by the claims are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. Applicant's disclosure teaches that the AL1 and either of the AL12 or AL13 antibodies are required to determine if one has an antibody reacting to any of the other epitopes of a pleiotrophin protein classed by applicant as "type III" (see e.g. page 18).

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated AL1, 3B10, 4B2, 10, 17, 24, 25, 26, 27, 31, 41, 50, 60, 87, 3-4A, 3-11F, and either of AL12 or AL13 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the claimed cell line; the cell lines which produce the chemically and functionally distinct antibodies claimed and/or required by the invention as claimed; and/or, the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions,

can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the hybridomas designated AL1, 3B10, 4B2, 10, 17, 24, 25, 26, 27, 31, 41, 50, 60, 87, 3-4A, 3-11F, and either of AL12 or AL13. A suitable deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) the deposits were viable at the time of deposit; and,
(e) the deposits will be replaced if they should ever become non-viable.

Applicant is also reminded that information regarding the deposits, such as the name and address of the depository, in addition to the accession numbers of the deposits and the date(s) of the deposits, **must** be added to the specification by means of filing an amendment as required by 37 CFR § 1.809(d).

Claims 40, 46, 47, and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with that as claimed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Other than antibodies comprising all of the relevant complementarity determining regions (CDRs) of SEQ ID NOS: 3 and 8 disclosed by applicant (SEQ ID NOS: 5-7 and 10-12) in the proper site on an appropriate antibody heavy or light chain framework, respectively, the skilled artisan cannot envision the detailed structure of the full scope of the encompassed polypeptides as are claimed. Applicant has reduced to practice and taught as functional in the invention only intact variable antibody chains as disclosed, such as SEQ ID NOs: 3 and 8, with the CDRs at specific regions of the chains and both such heavy and light chains forming the functional antibody. Moreover, claims not containing elements critical or essential to the practice of the invention, such as antibodies or antibody fragments having all of the relevant functional complementarity determining regions (CDRs) in the proper site on an appropriate antibody heavy or light chain framework, are not enabled by the disclosure. See *In re Mayhew*,

527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc Natl Acad Sci USA 79: 1979, 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Therefore, absent further written description and guidance from applicant, one would not be assured of the ability to make and use the invention without the requisite structural relationships of complementarity determining regions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 39 and claims dependent thereupon, "The" antibody or fragment lacks antecedent basis. It is not clear what applicant intends as encompassed by a "type III epitope" or a "biological activity" of pleiotrophin.

Claim 40 is vague in the absence of recitation of deposit accession number(s) to clearly identify the claimed antibody/hybridoma species because, absent the recitation of deposit accession numbers, it is not clear what structure and properties are encompassed by the named antibodies. In claim 40, "the same epitope" lacks antecedent basis and it is entirely unclear what is within the metes and bounds of the invention because it is not clear what applicant intends as

encompassed by "substantially" the same epitope. What degree of binding reduction is sufficient for "substantial" binding competition? In alternative (c), improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

In claims 41, 46, 47, 49, 50, and 52, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

In claims 42-45, it is not clear what is being further limited other than the intended use of the antibody.

In claim 55, "said" protein lacks antecedent basis. The interrelationships of the steps in the method of production are not clear because there is no connection between the step of isolating a monoclonal antibody and any of the other steps.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,
except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claims 39-46, 49, 50, 53, and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jäger et al. (Int. J. Cancer 73: 537, 1997) in light of the instant disclosure.

Jäger et al. teach an antibody to pleiotrophin which inhibits the biological activity of the protein. In light of the instant disclosure, the antibody binds to at least one epitope as instantly defined.

Claim 52 is rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by von Büdingen et al. (US 6,569,431). SEQ ID NO: 8 of the reference comprises SEQ ID NO: 12 as instantly claimed.

Claim 55 is rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by Paliard et al. (US 6,562,346).

Paliard et al. teach the elicitation of monoclonal antibodies by immunization of a mammal with fusion proteins comprising a protein of interest and at least one T cell epitope, hybridization of B cells obtained from the immunized animal to a myeloma cell, and identification and culture of relevant hybridomas (see e.g. col. 16).

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Roes et al. (J. Immunol. Meth. 183:231-237, 1995) teach immunization of knockout mice with the knockout gene product for production of monoclonal antibodies.

Amet et al. (Mol. Cell. Neurosci. 17:1014, 2001) teach pleiotrophin knockout mice.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JLG/
James L. Grun, Ph.D.
July 6, 2007

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